Godina 2015. u kardiologiji: slikovni prikazi

The year in cardiology 2015: imaging

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Uvod

Tijekom 2015. godine provedeno je nekoliko značajnih istraživanja koja su usredotočena na prognostičke implikacije pojedinih neinvazivnih metoda oslikavanja. Napredak u oslikavanju srca magnetnom rezonancijom i postupcima nuklearnog oslikavanja omogućio je prikaz aterosklerotskog procesa i vulnerabilnog plaka neinvazivnim postupcima. Trodimenzionalna ehokardiografija i višeslojna kompjutorizirana tomografija također su unaprijedili naše razumijevanje bolesti srčanih zalistaka. U tijeku je prikupljanje podataka o integriranim neinvazivnim metodama oslikavanja u kliničkoj praksi (tzv. fuzijske tehnike oslikavanja) za koje se očekuje veća uporaba u budućnosti. Ovaj pregledni članak sažima odabrane članke o prognostičkom utjecaju suvremenih neinvazivnih tehnika oslikavanja i o tehnološkim inovacijama.

Ehokardiografija

Godine 2015. godine objavljene su nove preporuke za ehokardiografsku kvantifikaciju srčanih šu-

Preamble

Prognostic implications of several non-invasive imaging techniques have been the focus of some landmark studies published in 2015. Non-invasive characterization of atherosclerosis processes and vulnerable plaques have been possible with advances in cardiac magnetic resonance imaging and nuclear imaging techniques. In addition, 3-dimensional echocardiography and multidetector-row computed tomography have improved our understanding of valvular heart disease. Finally, data on the clinical role of integration of non-invasive imaging techniques (fusion imaging) are accumulating and its use is expected to increase in the coming years. The current review provides a summary of selected articles on prognostic impact of current non-invasive imaging techniques and technological innovations.

Echocardiography

In 2015, the new recommendations for cardiac chamber quantification using echocardiogra-

pljina u odraslih osoba koje sadržavaju ažurirane normativne vrijednosti za sve četiri srčane šupljine na temelju više baza podataka velikoga broja zdravih osoba.[1] Osim toga, ovaj službeni dokument sadržava referentne vrijednosti za kvantifikaciju srčanih šupljina trodimenzionalnom (3D) ehokardiografijom i oslikavanjem deformacije miokarda nastale naprezanjem. Ovi normativni podatci omogućuju razlikovanje normalnih i patoloških rezultata. Iz kliničke je perspektive najvažnija definicija razine abnormalnosti (blaga, umjerena ili značajna). U preporukama se navode teškoće u određivanju praga između pojedinih razina abnormalnosti, a prikazuje se i značenje vrijednosti temeljenih na kliničkom iskustvu samo za veličinu, funkciju i masu lijeve klijetke (LK) te volumen lijevog atrija (LA).

U tijeku je prikupljanje podataka koji pokazuju prognostičke vrijednosti globalnoga longitudinalnog naprezanja lijeve klijetke (GLS). Nedavno objavljena metaanaliza 16 istraživanja (n = 5721), koja obuhvaća različite bolesti srca (zatajivanje srca, akutni infarkt miokarda te bolest srčanih zalistaka i dr.), koja je dokazala da je prognostička vrijednost GLS-a značajnija od istisne frakcije lijeve klijetke (LVEF).[2] Nakon multivarijatne analize, svaka promjena jedne standardne devijacije (SD) u vrijednostima GLS-a neovisno je povezana s ukupnom smrtnosti (HR 0,50; 95 % CI 0,36 – 0,69) u usporedbi s LVEF-om (HR 0,81; 95% CI 0,72 – 0,92), što je pokazalo da je vrijednost HR-a za svaku standardnu devijaciju promjene u GLS-u bio 1,62 puta veći od LVEF-a (95 % CI 1,13 – 2,33; P = 0,009). Regionalno longitudinalno naprezanje LK u pacijenata nakon infarkta miokarda klinički je možda značajnije od GLS-a. Podanaliza studije VALIANT, kojom je bilo obuhvaćeno 248 pacijenata sa sistoličkom disfunkcijom LK i/ili zatajivanjem srca (ZS) dokazala je da je regionalno longitudinalno naprezanje LK bilo oslabljeno čak i u segmentima s normalnim indeksom pokretljivosti stijenki u usporedbi sa zdravim pacijentima (–10,4 ± 5,2 %, odnosno –20,0 ± 7,6, P < 0,001).[3] Segmenti s abnormalnim longitudinalnim naprezanjem definirani su kao segmenti s vrijednosti naprezanja višom (tj. manje negativnom) od 95 % percentila odgovarajućih normalnih kontrolnih segmenata. Veći broj segmenata LK s patološkim regionalnim naprezanjem bio je povezan s povećanim rizikom od ukupne smrtnosti (HR 1,42; 95 % CI 1,06 – 1,90, P < 0,001).

Ehokardiografska analiza pacijenata sa ZS-om koji su kandidati za resinkronizacijsko liječenje (CRT) i dalje je predmet interesa. Rezultati subanalize studije EhoCRT (CRT pri zatajenju srca s uskim QRS kompleksom), ehokardiografskim praćenjem pokazali su da je 77 % od 614 pacijenata nakon razdoblja praćenja od šest mjeseci imalo kontinuiranu ili pogoršanu disinkroniju LK (≥ 130 msek. mjereno *speckle tracking* ehokardiografijom ili ≥ 80 msek. koristeći se tkivnim doplerom).[4] Kontinuirana ili pogoršana disinkronija LK povezana je s povećanim rizikom od ukupne smrtnosti i hospitalizacijom zbog ZS-a (HR 1,54, 95 % CI 1,03 – 2,3; P = 0,02). Takvi podatci potvrđeni su i u PREDICT-CRT, velikom multicentričnom registru.[5] "Ljuljanje" vrha LK i septalni "bljesak" uočeni ehokardiografskim nalazom znakovi su disinkronije LK uzrokovane blokom lijeve grane. U 1060 pacijenata korekcija za ehokardiografske varijable "ljuljanja" vrha LK i septalnog "bljeska" nakon 6 – 12 mjeseci liječenja primjenom CRT-a bila je povezana s reverznim remodeliranjem LK i većom vjerojatnošću preživljenja pri dugoročnom praćenju. S druge

phy in adults were published providing updated normative values for all four cardiac chambers based on multiple databases compiling data from a large number of normal subjects.[1] In addition, this position document includes reference values for chamber quantification with three-dimensional (3D) echocardiography and myocardial deformation with strain imaging. These normative data permit differentiation between normal and abnormal findings. From a clinical perspective however, definition of the degree of abnormality (mild, moderate, or severe) may be more meaningful. The document acknowledges the difficulties to determine cut-off values that define the degree of abnormality and provides experience-based partition values only for left ventricular (LV) size, function and mass, and for left atrial (LA) volume.

Data showing the prognostic value of LV global longitudinal strain (GLS) are accumulating. A recent meta-analysis pooling data from 16 studies (n = 5721), encompassing different cardiac diseases [heart failure, acute myocardial infarction (MI), and valvular heart disease among others], showed that the prognostic value of LV GLS exceeds that of LV ejection fraction (EF).[2] On multivariable analysis, each 1 standard deviation (SD) change in LV GS was independently associated with all-cause mortality (hazard ratio, HR 0.50; 95% CI 0.36–0.69) compared with LVEF (HR 0.81; 95% CI 0.72–0.92), indicating that the HR per each 1 SD change in LV GLS was 1.62 times greater than that of LVEF (95% CI 1.13–2.33; P = 0.009). In patients with MI, regional LV longitudinal strain may clinically be more meaningful than GLS. A subanalysis of the VALIANT (Valsartan in Acute Myocardial Infarction Trial) trial including 248 patients with LV systolic dysfunction, heart failure, or both demonstrated that regional LV longitudinal strain was significantly impaired even in segments with normal wall motion score index compared with healthy controls (–10.4 ± 5.2% vs. –20.0 ± 7.6, P < 0.001).[3] Abnormal longitudinal strain segments were defined as having a strain value higher (less negative) than the 95% percentile of corresponding normal control segments. An increasing number of LV segments with abnormal regional strain was associated with an increased risk of all-cause mortality (HR 1.42; 95% CI 1.06–1.90, P < 0.001).

Echocardiographic assessment of heart failure patients who are candidates for cardiac resynchronization therapy (CRT) remains of interest. Results of the EchoCRT (CRT in heart failure with narrow QRS complex) substudy showed that 77% of the 614 patients with echocardiographic follow-up at 6 months had persistent or worsened LV dyssynchrony (≥130 ms as measured with STE or ≥80 ms using tissue Doppler imaging).[4] The presence of persistent or worsened LV dyssynchrony was associated with increased risk of all-cause mortality and heart failure hospitalization (HR 1.54, 95% CI 1.03–2.3; P = 0.02). These results were also observed in the large multicentre registry PREDICT-CRT.[5] Left ventricular apical rocking and septal flash visualized on echocardiography are markers of left bundle branch block-induced LV dyssynchrony. In 1060 patients treated with CRT, correction of apical rocking and septal flash at 6–12 months echocardiography was associated with LV reverse remodelling and better survival at long-term follow-up. In contrast, patients who still exhibited LV apical rocking or septal flash at follow-up showed less LV reverse remodelling and worse outcome.

strane, pacijenti u kojih je pri pregledu još uvijek bilo prisutno "ljuljanje" vrha LK ili septalni "bljesak" pokazivali su manje reverznog remodeliranja LK i lošiji ishod.

Prognostička vrijednost funkcije desne klijetke (DK) također je analizirana u nekoliko istraživanja.[6,7] Melenovsky *i sur.* dokazali su u 96 ispitanika sa ZS-om i očuvanom LVEF usporedo s 46 kontrolnih ispitanika kojima je učinjena na temelju kliničke slike indicirana desnostrana kateterizacija srca i transtorakalna ehokardiografija da su muški spol, LVEF, fibrilacija atrija, koronarna bolest srca i sistolički arterijski tlak neovisno povezani s disfunkcijom DK (koja je definirana kao promjena ejekcijske frakcije DK < 35 %) nakon prilagodbe za plućni arterijski tlak u DK.[6] Pacijenti s disfunkcijom DK imali su manju vjerojatnost preživljenja u sljedeće dvije godine u usporedbi s onima bez disfunkcije (56 prema 93 %). Disfunkcija DK najsnažnija je poveznica s ukupnom smrtnosti u modelu korigiranom za sistolički tlak u plućnoj arteriji (HR 2,2; 95 % CI 1,4 – 3,5; *P* = 0,001). Napredak u 3D *strain* prikazu omogućio je karakterizaciju remodeliranja DK u pacijenata s plućnom hipertenzijom.[7] Morfološki i funkcionalni podatci o DK u 92 pacijenta s plućnom hipertenzijom analizirani su novom 3D *motion tracking* ehokardiografijom. Na temelju krivulje tlak-volumen dobivenih kateterizacijom desnoga srca pacijenti su podijeljeni u tri skupine: prilagođena DK, prilagođena-remodelirana DK i nepovoljno remodelirana DK. Progresivno oštećenje EF DK i opće naprezanje uočeni su u svim trima skupinama, iako je skupina nepovoljno remodelirana DK imala najlošije vrijednosti. Pacijenti iz skupine s prilagođenom DK tijekom razdoblja od šest mjeseci pokazali su bolju stopu preživljavanja bez hospitalizacije, smrti ili transplantacije pluća u usporedbi s ostalim skupinama (HR 0,15; 95 % CI 0,07 – 0,3; *P* < 0,001), dok su pacijenti u skupini s nepovoljno

The prognostic value of right ventricular (RV) function was also evaluated in several studies.[6,7] In 96 patients with heart failure with preserved LVEF and 46 controls who underwent clinically indicated right-sided heart catheterization and transthoracic echocardiography, Melenovsky and coworkers showed that male gender, LVEF, atrial fibrillation, coronary artery disease (CAD), and systemic systolic blood pressure were independently associated with RV dysfunction (defined as RV fractional area change <35%) after adjusting for RV pulmonary arterial pressures.[6] Patients with RV dysfunction showed lower 2-year survival compared with patients without (56 vs. 93%). Right ventricular dysfunction was the strongest associate of all-cause mortality in a model corrected for systolic pulmonary artery pressure (HR 2.2; 95% CI 1.4–3.5; *P* = 0.001). Advances in 3D strain imaging have allowed characterization of RV remodelling in patients with pulmonary hypertension.[7] Right ventricular morphological and functional data of 92 patients with pulmonary hypertension were analysed with novel 3D motion tracking echocardiography. Based on pressure–volume loops obtained during right-sided heart catheterization, patients were divided into three groups: RV adapted, RV adapated-remodelled, and RV adverse-remodelled. A progressive impairment in RVEF and global area strain was observed across the three groups with the RV adverse-remodelled group having the worst values. Patients within the RV adapted group showed better 6-month free-survival from hospitalization, death, or lung transplantation compared with the other groups (HR 0.15; 95% CI 0.07–0.3; *P* < 0.001), whereas patients within the RV adverse-remodelled group showed the worst outcome (HR 2.2; 95% CI 0.91–5.39, *P* = 0.004).

Three-dimensional echocardiography is increasingly used in heart valve disease. Debonnaire and coworkers demon-

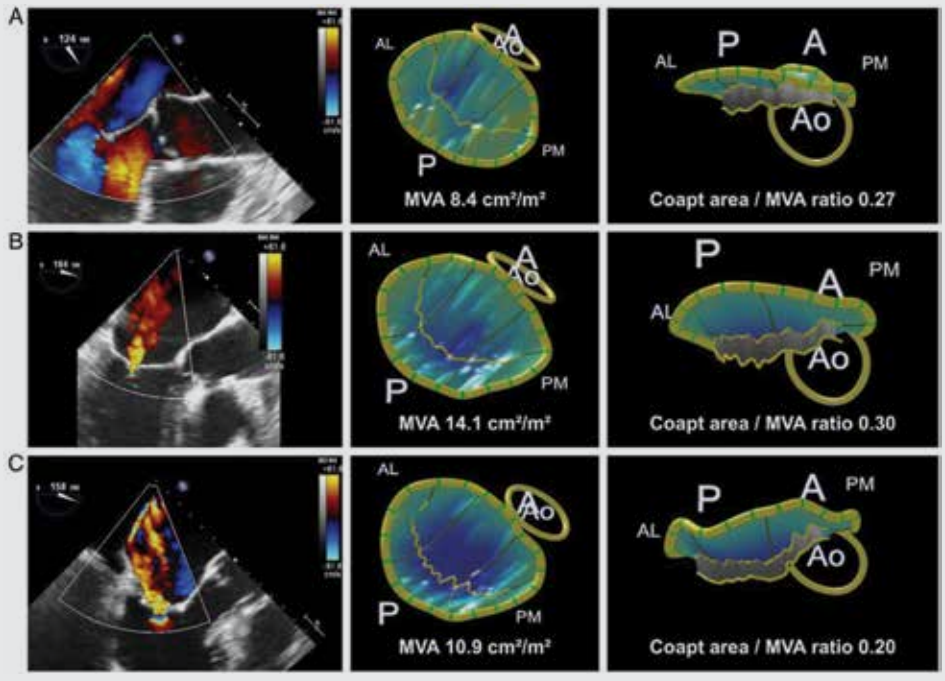

FIGURE 1. Examples of mitral valve leaflet remodelling using 3D transoesophageal echocardiography. (A) Example of an individual without functional mitral regurgitation. (B) Examples of two patients with mild (B) and severe functional mitral regurgitation (C), both secondary to inferior infarction. Note the larger mitral valve area (MVA) as well as the coaptation area to MVA ratio in the patient with mild vs. the patient with severe functional mitral regurgitation.

A = anterior; AL = anterolateral; Ao = aorta; P, posterior; PM = posteromedial. Reproduced with permission from Debonnaire *et al.*[8]

remodeliranom DK imali najlošiji ishod (HR 2,2; 95 % CI 0,91 – 5,39; *P* = 0,004).

Trodimenzionalna se ehokardiografija sve više primjenjuje u liječenju bolesti srčanih zalistaka. Debonnaire *i sur.* pokazali su da trodimenzionalna transezofagealna ehokardiografija može zadovoljavajuće opisati remodeliranje kuspisa mitralnih zalistaka u pacijenata s disfunkcijom LK i funkcionalnom mitralnom regurgitacijom (MR).[8] Nedostatno remodeliranje kuspisa s obzirom na anularnu dilataciju i dilataciju LK dovodi do reducirane koaptacije, koja je neovisno povezana s težinom MR-a u pacijenata s funkcionalnom MR. **Slika 1** prikazuje različite primjere remodeliranja kuspisa mitralnog zalistka u pacijenata s funkcionalnim MR-om i u pacijenata bez MR-a. Clavel *i sur.* trodimenzionalnom su transezofagealnom ehokardiografijom procijenili 49 pacijenata s degenerativnom bolešću mitralnog zalistka.[9] Autori su pokazali važne razlike u remodeliranju LK, anularnim dimenzijama te dimenzijama zalistaka povezanim s razlikama u težini MR-a između pacijenata s fibroelastičnom bolesti i difuznom miksomatoznom degeneracijom.

Topilsky *i sur.* pokazali su malu, ali značajnu vrijednost kvantifikacije trikuspidne regurgitacije (TR) za procjenu preživljenja.[10] U 353 pacijenta s različitim stupnjevima izolirane funkcionalne TR, efektivna regurgitirajuća površina ušća (EROA) izračunana je metodom proksimalnog toka konvergencije. Vrijednost EROA ≥ 40 mm^2 bila je pokazatelj jake TR, a pronađena je u 40 % pacijenata. Tijekom prosječnog razdoblja praćenja od 5,8 godina 82 pacijenta su preminula. Vrijednost EROA ≥ 40 mm^2 bila je neovisno povezana s ukupnom smrtnosti (HR 2,95; 95 % CI 1,67 – 5,19; *P* < 0,001) nakon korekcije za klinička obilježja, LVEF, veličinu DK, funkciju DK i sistolički tlak u DK.

Kompjutorizirana tomografija

Valenti *i sur.* objavili su dugoročne prognostičke podatke za količinu kalcija u krvnim žilama (CACS) u 9715 asimptomatskih pacijenata koji su bili praćeni tijekom 14,6 godina: CACS se pokazao najkorisnijim kao prognostički čimbenik smrtnog ishoda, neovisno o procjeni rizika prema Framinghamu (FRS) ili NCEP ATP III kategoriji rizika.[11] Vrijednosti CACS-a od 0 povezana je s nepromjenjivo niskom stopom smrtnosti od 4,7 % (tj. 0,3 % godišnje u prosjeku) te stoga produžava razdoblje značenja nulte vrijednosti CACS-a kroz razdoblje od gotovo 15 godina, posebice u pacijenata s niskim i srednjim rizikom, neovisno o spolu. U nedavno objavljenom radu iz CONFIRM studije istraživači su verificirali da CT koronarna angiografija (CTCA) u 3217 asimptomatskih pacijenata ima značajniju prognostičku vrijednost u usporedbi s rezultatom procjene rizika prema FRS-u samo u pacijenata s vrijednostima CACS-a > 100 (netopoboljšanje ponovne reklasifikacije 0,62; *P* < 0,001), ali ne i u pacijenata s vrijednostima CACS-a ≤ 100.[12] No, u slučaju visokih i vrlo visokih podskupina CACS-a (tj. > 400 i > 1000) prognostička je vrijednost CTCA ponovno izgubljena, vjerojatno zbog manje pouzdanog tumačenja CTCA. Zaključci o tim podskupinama ipak su bili ograničeni zbog niskoga broja ispitanika i stope događaja.

U kohortnoj studiji VISION bila je procijenjena vrijednost CTCA za predviđanje rizika od kardiovaskularnih komplikacija u nekardijalnim kirurškim zahvatima.[13] Bilo je uključeno je

strated that 3D transoesophageal echocardiography could adequately depict mitral valve leaflet remodelling in patients with LV dysfunction and functional mitral regurgitation (MR).[8] Insufficient leaflet remodelling relative to annular and LV dilatation resulted in reduced coaptation, which was independently associated with MR severity in patients with functional MR. **Figure 1** illustrates different examples of mitral valve leaflet remodelling in patients with functional MR and patients without MR. Clavel *et al.* used 3D transoesophageal echocardiography to evaluate 49 patients with degenerative mitral valve disease.[9] The authors demonstrated important differences in LV remodelling, annular, and valvular dimensions, associated with differences in MR severity between patients with fibro-elastic deficiency and diffuse myxomatous degeneration.

Finally, the incremental value of quantification of tricuspid regurgitation (TR) to predict survival was demonstrated by Topilsky *et al.*[10] In 353 patients with various degrees of isolated functional TR, the effective regurgitant orifice area (EROA) was calculated with the proximal flow convergence method. An EROA ≥40 mm^2 defined severe TR and was observed in 40% of patients. During a mean follow-up of 5.8 years, 82 patients died. An EROA ≥40 mm^2 was independently associated with all-cause mortality (HR 2.95; 95% CI 1.67–5.19; *P* < 0.001) after adjusting for clinical characteristics, LVEF, RV size, RV function, and RV systolic pressure.

Computed tomography

Very long-term prognostic data for coronary artery calcium score (CACS) were published by Valenti and coworkers in 9715 asymptomatic subjects followed for 14.6 years: CACS emerged as the strongest predictor of death, and was independent from Framingham risk score (FRS) or National Cholesterol Education Program Adult Treatment Panel III risk category.[11] A CACS = 0 was associated with an invariably low death rate of 4.7% (i.e. 0.3%/year on average), and thereby extends the warranty period of zero CACS over a period of almost 15 years, particularly in low and intermediate risk patients, and regardless of gender. In a recent publication from the COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter registry, investigators observed in 3217 asymptomatic subjects that CT coronary angiography (CTCA) possessed incremental prognostic value over FRS only in patients with a CACS >100 (net reclassification improvement 0.62, P < 0.001), but not among those with CACS ≤100.[12] However, in high and very high CACS subgroups (i.e. >400 and >1000), the incremental value of CTCA was lost again, probably through less reliable CTCA interpretation. However, conclusions in these subgroups were limited due to low sample sizes and event rates.

The Coronary computed tomography angiography (CTA) vascular events in non-cardiac surgery patients cohort evaluation (VISION) study assessed the value of CTCA for predicting the risk of cardiovascular complications of non-cardiac surgery.[13] A total of 955 patients with vascular risk factors were included, of which 74 (8%) suffered a perioperative event (cardiovascular death/MI). Computed tomography coronary

955 pacijenata s vaskularnim čimbenicima rizika, među kojima je njih 74 (8 %) pretrpjelo perioperativne događaje (kardiovaskularna smrt / infarkt miokarda). Rezultati CTCA pružili su neovisne prognostičke podatke s obzirom na alate za procjenu srčanog rizika sa sve većim HR za neopstrukcijske (HR 1,51, *P* = 0,30), opstrukcijske (HR 2,05, *P* = 0,076) i izrazito opstrukcijske (HR 3,76, *P* < 0,001) bolesti. No, c-indeks je samo povećan s 0,62 na 0,66 nakon dodavanja CTCA u modele predviđanja rizika, uglavnom zbog reklasifikacije velikoga broja pacijenata (~10 %) u kategoriju većeg rizika, koji ipak nisu pretrpjeli nijedan događaj. Stoga rezultati studije VISION upućuju na mogućnost prekomjerne procjene visokog rizika primjenom CTCA u usporedbi s alatima koji klinički procjenjuju rizik.

Predmet je rasprave i dijagnostički rezultat CT-a za isključenje *triple rule-out* (TRO) – infarkta miokarda, plućne embolije i disekcije aorte u pacijenata s akutnim bolom u prsima, istražen na temelju baze podataka *Advanced Cardiovascular Imaging Consortium* u 12 834 pacijenta.[14] Dijagnostički je rezultat bio sličan za TRO u usporedbi s CTCA (17,4 prema 18,3 %; *P* = 0,37), a uglavnom je proveden detekcijom koronarne bolesti srca (15,5 prema 17,2 %; *P* = 0,093), dok je TRO CT imao nešto više dijagnoza plućne embolije (1,1 prema 0,4 %; *P* = 0,004) i disekcije aorte (1,7 prema 1,1 %; *P* = 0,046), ali s višom prosječnom radijacijom (9,1 prema 6,2 mSv; *P* < 0,0001) i prosječnom dozom kontrasta (113 ± 6 prema 89 ± 17 mL; *P* < 0,0001) te višom učestalosti nedijagnostičke kvalitete slike (9,4 prema 6,5 %; *P* < 0,0001). Premda TRO CT može biti koristan u određenih pacijenata (nakon što se pažljivo prouče pojedini rizici od infarkta miokarda / plućne embolije / disekcije aorte), to se istraživanje ne može u svim slučajevima primijeniti u odjelima hitne pomoći.

U 2015. željno su se iščekivali rezultati dvaju velikih CT istraživanja: u prospektivnom multicentričnom istraživanju za procjenu bolova u prsnom košu: 10 003 simptomatska pacijenta s intermedijarnom predtestnom vjerojatnošću koronarne bolesti srca (KBS) randomizirana su za strategiju početnog anatomskog testiranja primjenom CTCA u odnosu prema uobičajenom funkcijskom testiranju (67% testiranje opterećenjem uz primjenu radiofarmaka, 23% stres ehokardiografija, 10% ergometrija).[15] Praćenjem nakon 25 mjeseci nisu registrirane razlike u primarnom zajedničkom ishodu (smrt, infarkt miokarda, hospitalizaciji zbog nestabilne angine ili većih proceduralnih komplikacija). No, CTCA je rezultirao manjom učestalošću kateterizacija srca kod neopstruktivne KBS (3,4 prema 4,3 %; *P* = 0,02), iako je više pacijenata u skupini CTCA bilo na kateterizaciji (12,2 prema 8,1 %) i revaskularizaciji (6,2 prema 3,2 %; *P* < 0,001) unutar 90 dana od randomizacije. U studiji *Scottish COmputed Tomography of the HEART* bilo je 4146 pacijenata randomizirano u skupine za standardno liječenje (uključujući kliničku procjenu i ergometriju) uz CACS te CTCA, odnosno samo standardno liječenje.[16] Uporaba CTCA povećala je dijagnostičku sigurnost (RR 1,79; *P* < 0,001) za primarni ishod angine zbog KBS-a, odgodila 121 funkcijsko testiranje i 29 invazivnih angiograma te rezultirala većim promjenama liječenju u sekundarnoj prevenciji. Nakon razdoblja praćenja od 1,7 godina zamjetno je brojčano (premda neznačajno) smanjenje od 38 % u zajedničkom ishodu od smrti od KBS-a / infarkta miokarda u skupini s primjenom CTCA (*P* = 0,053).

Frakcijska rezerva protoka primjenom CT-a (FFR_{CT}) i dalje je predmet interesa u 2015. godini, što je vidljivo iz novog rada iz angiography findings provided independent prognostic information over revised cardiac risk indices with increasing HRs for non-obstructive (HR 1.51, P = 0.30), obstructive (HR 2.05, P= 0.076), and extensive obstructive (HR 3.76, P < 0.001) disease. However, the c-index increased only from 0.62 to 0.66 when adding CTCA to the clinical risk prediction models, mostly because of reclassification of a sizable number of patients (10%) into a higher-risk category who would not suffer any subsequent event. Thus, the results of the coronary CTA VISION raise concerns about overestimation of risk by CTCA compared with clinical risk indices.

The diagnostic yield of CT for triple rule-out (TRO) of MI, pulmonary embolism (PE), and aortic dissection (AD) in patients with acute chest pain is a debated issue, and was investigated in the Advanced Cardiovascular Imaging Consortium database in 12 834 patients.[14] The overall diagnostic yield was similar for TRO CT compared with CTCA only (17.4 vs. 18.3%; P = 0.37) and was driven mainly by CAD detection (15.5 vs. 17.2%, P = 0.093); TRO CT, however, yielded slightly more PE (1.1 vs. 0.4%; P = 0.004) and AD (1.7 vs. 1.1%; P = 0.046) diagnoses, although at a higher median radiation (9.1 vs. 6.2 mSv; P < 0.0001) and mean contrast dose (113 ± 6 vs. 89 ± 17 mL; P < 0.0001), and higher non-diagnostic image quality rate (9.4 vs. 6.5%; P < 0.0001). Thus, although TRO CT may be useful in selected patients (after careful consideration of individual MI/PE/AD risks), the study does not support its indiscriminate use in emergency departments.

The results of two large randomized CT studies were eagerly awaited in 2015: in the prospective multicenter imaging study for evaluation of chest pain trial, 10 003 symptomatic patients with intermediate CAD pretest probability were randomized to a strategy of initial anatomical testing with CTCA vs. traditional functional testing (67% stress nuclear, 23% stress echocardiography, and 10% exercise ECG).[15] At 25 months follow-up, there were no differences in the primary endpoint of death, MI, hospitalization for unstable angina, or major procedural complications. However, CTCA resulted in fewer catheterizations showing no obstructive CAD (3.4 vs. 4.3%, P = 0.02), although more patients in the CTCA group underwent catheterization (12.2 vs. 8.1%) and were revascularized (6.2 vs. 3.2%, P < 0.001) within 90 days of randomization. The Scottish COmputed Tomography of the HEART trial randomized 4146 patients to standard care (SC) (including clinical assessment and exercise ECG) plus CACS and CTCA vs. SC alone.[16] The use of CTCA increased diagnostic certainty [relative risk (RR) 1.79; P < 0.001) for the primary endpoint of angina due to CAD, resulted in cancellation of 121 functional tests and 29 invasive angiograms, and more changes in preventive and antianginal drug therapies. At follow-up of 1.7 years, there was a numerical (although not significant) 38% reduction of the composite endpoint of CAD death/MI in the CTCA group (P = 0.053).

Computed tomography-derived fractional flow reserve (FFR_{CT}) continues to raise interest in 2015 through its latest publication, the Prospective LongitudinAl Trial of FFRct: Outcome and Resource IMpacts study.[17] In this trial, 584 symptomatic patients with intermediate CAD pretest probability were prospectively (but not randomly) assigned to receive either usual testing (n = 287, i.e. non-invasive testing or in-

PLATFORM studije.[17] U navedenom istraživanju u 584 pacijenta s intermedijarnom predtestnom vjerojatnošću za KBS prospektivno je (ali ne nasumično) bila učinjena uobičajena obrada (*n* = 287, npr. neinvazivno testiranje ili invazivna koronarna angiografija, ICA) ili CTCA (*n* = 297) s dodatnim FFR_{CT} ako je indicirano. Među onima s planiranom ICA (*n* = 380), primjena FFR_{CT} dovela je do znatnog smanjenja broja invazivnih kateterizacija u onih bez nalaza opstruktivne KBS (sa 73 na 12%) te je izbjegnuta primjena ICA u 117 (61 %) pacijenata, pri čemu nisu registrirane razlike u skupini pacijenata s planiranim neinvazivnim testiranjem (**slika 2**). Premda istraživanje PLATFORM nije bilo randomizirano, pružilo je suvremeni pregled trenutačne uporabe dijagnostičkih 'platformi' za dijagnostiku te govori o pretjeranoj uporabi ICA u pacijenata s intermedijarnom vjerojatnosti KBS-a, što bi se moglo smanjiti širom uporabom FFR_{CT}. Zanimljivo je da je nedavno objavljena subanaliza studije PLATFORM dokazala da je uporaba FFR_{CT} povezana sa smanjenjem cijene u iznosu od 3391 dolar u usporedbi s ICA, dok razlike u troškovima između strategije FFR_{CT} i uobičajene dijagnostike (neinvazivnog testiranja) nisu bile značajne (7047 prema 8422 dolara).[18] No u skupini podvrgnutoj neinvazivnoj dijagnostici pacijenti u kojih je primijenjen FFR_{CT} pokazali su bolje rezultate na upitnicima o kvaliteti života u usporedbi s pacijentima koji su primali uobičajenu skrb, dok u invazivnoj skupini nije bilo razlike između FFR_{CT} i ICA.

Magnetna rezonancija srca

Analiza plakova u koronarnim arterijama primjenom magnetne rezonancije (MRI) bez kontrastnoga sredstva s T1 mjerenom slikom omogućila je nove uvid u patofiziologiju ozljede

vasive coronary angiography, ICA) or CTCA (n = 297) with additional FFR_{CT} where requested. Among those with intended ICA (n = 380), FFR_{CT} resulted in a significant reduction in the number of invasive catheterizations showing no obstructive CAD (from 73 to 12%) and avoided ICA in 117 (61%) patients, while no differences were noted in the group of patients with intended non-invasive testing (**Figure 2**). Although the PLATFORM study was not randomized, it provides a contemporary snapshot of the current use of diagnostic 'platforms' for CAD work-up, and suggests overuse of ICA in intermediate probability patients which could be reduced by wider use of FFR_{CT}. Interestingly, the recently published PLATFORM substudy demonstrated that the use of FFR_{CT} was associated with $3391 costs reduction compared with ICA, whereas differences in downstream costs between FFR_{CT} strategy and usual care (non-invasive testing) were not significant ($7047 vs. $8422, respectively).[18] However, in the non-invasive arm, patients undergoing FFR_{CT} showed better scores on quality-of-life questionnaires compared with patients undergoing usual care, whereas in the invasive arm, there were no differences between FFR_{CT} and ICA.

Cardiac magnetic resonance

Characterization of coronary artery plaques with non-contrast T1-weighted magnetic resonance imaging (MRI) has provided novel insights into the pathophysiology of percutaneous coronary intervention (PCI)-related myocardial injury, a procedural complication which has important prognostic implications.[19] Seventy-seven patients with stable angina and significant coronary artery lesions (>70% stenosis on

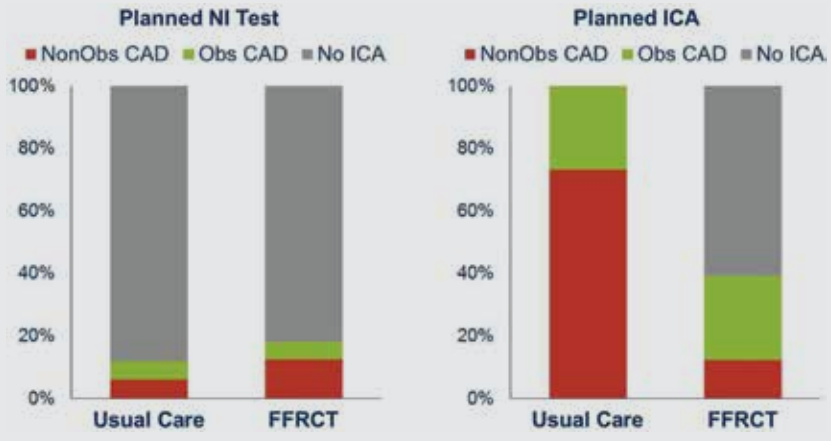

FIGURE 2. The PLATFORM (Prospective LongitudinAl Trial of FFRct: Outcome and Resource IMpacts) study compared FFR_{CT} as gatekeeper for invasive coronary angiography with direct angiography (right panel), as well as FFR_{CT} vs. routine non-invasive testing as gatekeeper for invasive angiography (left panel). In the patients with planned invasive coronary angiography (right panel), the use of FFR_{CT} as gatekeeper avoided invasive coronary angiography in 61%, and reduced the percentage of non-obstructive coronary artery lesions from 73 to 12%, whereas there were no differences in percentage of non-obstructive lesions on invasive angiography in the patients undergoing planned non-invasive testing (left panel). NI, non-invasive; ICA, invasive coronary angiography; Obs CAD, obstructive coronary artery disease; FFR_{CT}, computation of fractional flow reserve from coronary computed tomographic angiography data. Reprinted from Douglas *et al.*[17]

miokarda povezane s perkutanom koronarnom intervencijom (PCI) – proceduralne komplikacije s važnim prognostičkim implikacijama.[19] U 77 pacijenata sa stabilnom anginom i značajnim lezijama na koronarnim arterijama (> 70% stenoze na koronarnoj angiografiji) učinjena je MRI s 1,5 T, i to 48 sati prije postupka PCI. Sastav koronarnoga plaka procijenjen je s pomoću MRI-ja s T1 mjerenom slikom bez primjene kontrasta. Plak visokog intenziteta (koji se smatra vulnerabilnim plakom) definiran je omjerom između koronarnoga plaka i intenziteta signala miokarda koji iznosi ≥ 1,4. Ozljeda miokarda povezana s PCI-jem definirana je vrijednostima hsTnT višim od 5 puta od 99-e percentile gornje referentne vrijednosti. Pacijenti s plakom visokog intenziteta (*n* = 31) u usporedbi s pacijentima bez plaka visokog intenziteta imali su veći plak, veću lipidnu zalihu, češće pozitivno remodeliranje, atenuaciju ultrazvukom te intrakoronarni tromb dokazan primjenom intravaskularnog ultrazvuka (**slika 3**). Važno je istaknuti da je prisutnost plaka visokog intenziteta povezana s većom učestalošću ozljede miokarda povezane s PCI-jem (58 prema 11%; *P* < 0,001). Potrebno je dodatno istražiti kako spomenuti podatci mogu utjecati na donošenje odluka i intervencijske strategije.[20]

U pacijenata koji su preživjeli akutni infarkt miokarda s elevacijom ST segmenta (STEMI) procjena veličine infarkta i mikrovaskularne opstrukcije primjenom MRI-ja srca pojačana kontrastom ima važnu prognostičku vrijednost. Zanimljivo je da varijable dobivene MRI-jem srca bez primjene kontrasta, poput primjene T1 mjerene slike, omogućuju karakterizaciju tkiva iz središta infarkta. Nakon infarkta miokarda povećava se sadržaj vode u ishemijskom području, što će dovesti do dužega nativnog vremena T1 mjerene slike. Carrick *i sur.* su u 300 invasive angiography) underwent 1.5T MRI 48 h prior to PCI and coronary plaque composition was assessed with non-contrast T1-weighted MRI. High-intensity plaques (considered vulnerable plaques) were defined by a 'coronary plaque to myocardium signal intensity' ratio of ≥1.4. Percutaneous coronary intervention-related myocardial injury was defined as an increased high-sensitivity cardiac troponin T >5 times the 99th percentile upper reference limit. Patients with high-intensity plaques (*n* = 31) showed greater plaque burden, larger lipid pool, more frequently positive remodelling, ultrasound attenuation, and intracoronary thrombus on intravascular ultrasound analysis, compared with patients without high-intensity plaques (**Figure 3**). Importantly, the presence of high-intensity plaques was associated with higher frequency of PCI-related myocardial injury (58 vs. 11%, *P* < 0.001). How this information may influence the decision making and interventional strategy needs further study.[20]

In survivors of ST-segment elevation acute MI (STEMI), assessment of infarct size and microvascular obstruction with contrast-enhanced CMR has important prognostic value. Interestingly, non-contrast CMR-derived parameters such as native T1 mapping permit characterization of the infarct core tissue. After MI, there is an increase in water content in the ischaemic area that will result in longer native T1 times. Carrick and coworkers investigated in 300 survivors of STEMI, the correlation between native T1 time of the infarct core, infarct size and microvascular obstruction and the prognostic implications of native T1 time in terms of LV adverse remodelling (≥20% increase in end-diastolic volume at 6 months follow-up), all-cause mortality and heart failure hospitalization.[21] Pa-

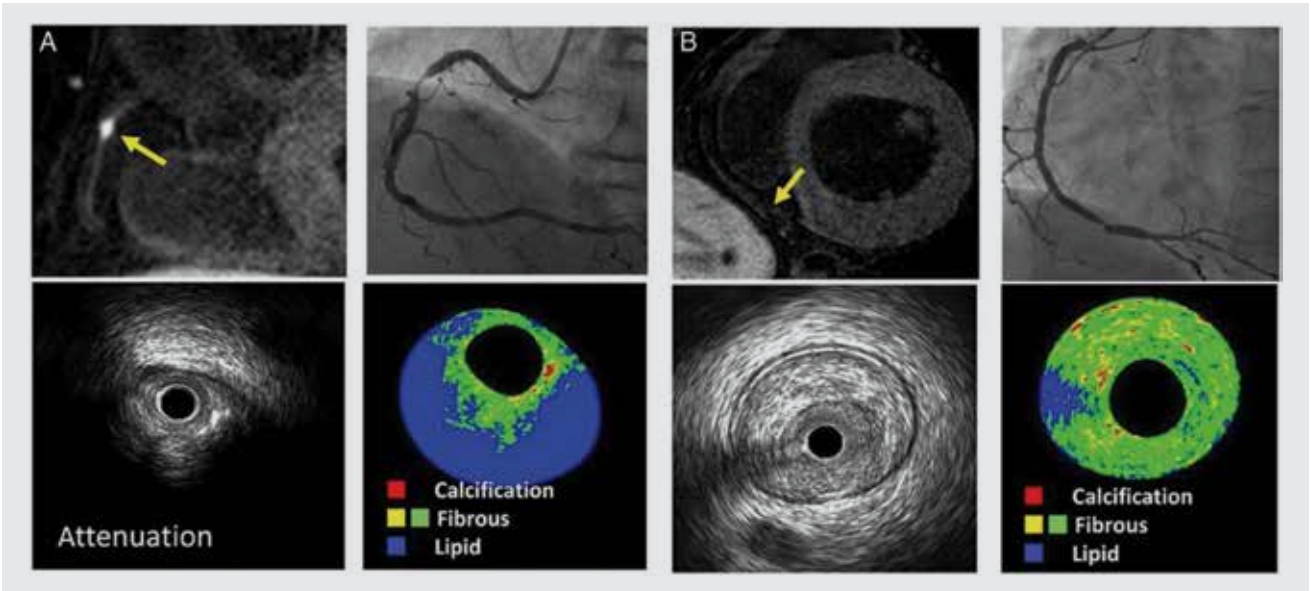

FIGURE 3. Coronary artery plaque characteristics assessed with non-contrast T_1-weighted cardiac magnetic resonance (CMR) imaging. (A) A significant stenosis of the mid-right coronary artery (on invasive angiography). On non-contrast T_1-weighted CMR (upper left corner), a high-intensity plaque can be observed (plaque to myocardium intensity ratio of 3.09) which shows attenuation and lipid-rich composition on intravascular ultrasound. (B) A significant stenosis of the distal right coronary artery and non-high-intensity plaque on CMR. Intravascular ultrasound with virtual histology shows a fibrous plaque. Reproduced with permission from Hoshi *et al.*[19]

pacijenata koji su preživjeli STEMI istražili korelaciju između nativnoga vremena T1 mjerene slike u središtu infarkta, veličine infarkta i mikrovaskularne opstrukcije te prognostičkih implikacija nativnoga vremena T1 u obliku nepovoljnog remodeliranja lijeve klijetke (≥ 20 %-tni porast dijastoličkoga volumena na kraju dijastole nakon 6 mjeseci praćenja), ukupne smrtnosti te hospitalizacije zbog ZS-a.[21] Pacijentima je učinjen *cine* MRI, nativno T1 i T2 mjerene slike, T2* i odgođeno bojenje gadolinijem (LGE) dva dana nakon infarkta miokarda i nakon praćenja od šest mjeseci. Nativno T1 vrijeme mjereno je u zoni infarkta, ozlijeđenog miokarda i u udaljenom miokardu. Zona infarkta definirana je kao miokard s vrijednostima piksela (T1 ili T2) > 2 SD od udaljene zone na sekvencijama MRI srca s T2 mjerenom slikom. Hipointenzivno središte infarkta definirano je kao područje unutar zone infarkta s vrijednostima piksela T1 < 2 SD od vrijednosti uočenih na periferiji zone infarkta. Nativni T1 središta infarkta u značajnoj je vezi s nativnim T2 (r = 0,42; P < 0,001). Nativne vrijednosti T1 u središtu infarkta povezane su s nepovoljnim remodeliranjem LK nakon praćenja od šest mjeseci (omjer vjerojatnosti 0,91 za svakih 10 msek. smanjenja, P = 0,061) te su neovisan prediktor ukupne smrtnosti ili hospitalizacije zbog ZS-a (HR 0,73; P < 0,001).

Primijenjeno je nekoliko varijabli dobivenih s pomoću MRI-ja srca kako bi se definirala i kvantificirala prisutnost fibroze miokarda (fokalne ili difuzne). Fokalna makroskopska fibroza najčešće se procjenjuje primjenom MRI-ja srca uz LGE, a difuzna fibroza može se karakterizirati izračunom ekstracelularnog volumena (ECV) nakon infuzije pripremljenoga kontrastnog sredstva ili primjene bolusa gadolinija, vrijednosti T1 nakon kontrastnoga sredstva i mapiranja vrijednosti (nativnog) T1 prije kontrastnoga sredstva. Promjene u intenzitetu signala LGE s T1 mjerenom slikom povezane su s ozljedom miokarda. Provedena je korelacija tih mjera s funkcijom LK i prognozom kod nekoliko bolesti srca.[22-26] U 65 pacijenata koji su dobili potencijalno kardiotoksičnu kemoterapiju vrijednost LVEF-a bila je znatno snižena nakon tri mjeseca liječenja (s 57 ± 1 na 54 ± 1%; P < 0,001), intenzitet miokardnog signala LGE s T1 mjerenjem bio je povećan (s 14,1 ± 0,6 na 15,9 ± 0,8; P = 0,046), a nije registrirano povećanje edema miokarda na sekvencijama MRI-ja s T2 mjerenjem.[22] Nije poznato mogu li te promjene poslužiti za predviđanje nepovratne ozljede miokarda nakon prekida kemoterapije. Prisutnost supkliničke difuzne fibroze miokarda bila je procijenjena mjerenjem vrijednosti ECV-a u 35 pacijenata s umjerenom i jakom asimptomatskom primarnom MR te očuvanom LVEF.[23] U usporedbi s kontrolnom skupinom, u pacijenata s MR registrirana je veća vrijednost ECV-a (0,32 ± 0,07 prema 0,25 ± 0,02; P < 0,01). Povećanje u vrijednosti ECV-a miokarda povezano je s većim krajnjim sistoličkim indeksom volumena LK (r = 0,62, P < 0,001) i indeksom volumena lijevog atrija (r = 0,41, P < 0,05), nižom vrijednosti LVEF-a (r = −0,6, P < 0,001) i lošijim funkcijskim kapacitetom prema mjerenjima maksimalne potrošnje kisika (r = −0,51, P < 0,005). Ellims *i sur.* u 139 pacijenata s hipertrofičnom kardiomiopatijom (HCM) istražili su korelaciju makroskopske fibroze miokarda (procijenjene s pomoću LGE MRI-ja srca) i difuzne fibroze miokarda (procijenjene mapiranjem T1 nakon primjene kontrastnoga sredstva) s funkcijom i genotipom LK.[24] Prisutnost LGE povezana je s LVEF i prisutnošću opstrukcije izgonskog trakta LK, dok su kraće vrijednosti mapiranja T1 nakon kontrastnoga sredstva

tients underwent cine CMR, native T1 mapping, T2 mapping, T2* mapping and late gadolinium contrast-enhanced (LGE) sequences 2 days after index MI and at 6 months follow-up. Native T1 times were measured in the infarct zone, injured myocardium, and remote myocardium. The infarct zone region was defined as myocardium with pixel values (T1 or T2) >2 SD from the remote zone on T2-weighted CMR sequences. The hypo-intense infarct core was defined as areas within the infarct zone with pixel T1 values <2 SD of the values observed in periphery of the infarct zone. Infarct core native T1 was significantly associated with native T2 (r = 0.42, P < 0.001). Native T1 values within the infarct core were associated with LV adverse remodelling at 6 months follow-up (odds ratio 0.91 per each 10 ms reduction, P = 0.061) and were independent predictors of all-cause mortality or heart failure hospitalization (HR 0.73, P < 0.001).

Several CMR-derived variables have been used to define and quantify the presence of myocardial fibrosis (focal or diffuse). While focal macroscopic fibrosis is commonly assessed with LGE CMR, diffuse fibrosis can be characterized by calculating the extracellular volume (ECV), after primed contrast infusion or administration of bolus of gadolinium, post-contrast T1-mapping values and pre-contrast (native) T1-mapping values. In addition, changes in T1-weighted LGE-signal intensity have been associated with myocardial injury. These measures have been correlated with LV function and prognosis in several cardiac diseases.[22–26] In 65 patients who underwent potentially cardiotoxic chemotherapy, LVEF decreased significantly after 3 months of therapy (from 57 ± 1 to 54 ± 1%, P < 0.001) while myocardial T1-weighted LGE-signal intensity increased (from 14.1 ± 0.6to 15.9 ± 0.8, P = 0.046) without an increase in myocardial oedema on T2-weighted CMR sequences.[22] Whether these changes may predict irreversible myocardial damage after withdrawal of chemotherapy, remains unknown. The presence of subclinical diffuse myocardial fibrosis was evaluated measuring the ECV in 35 patients with asymptomatic moderate and severe primary MR and preserved LVEF.[23] Compared with controls, patients with MR exhibited larger ECV (0.32 ± 0.07 vs. 0.25 ± 0.02, P < 0.01). Increasing myocardial ECV was significantly associated with larger LV end-systolic volume index (r = 0.62, P < 0.001) and left atrial volume index (r = 0.41, P < 0.05), lower LVEF (r = −0.6, P < 0.001) and worse functional capacity as measured with peak oxygen consumption (r = −0.51, P < 0.005). In 139 patients with hypertrophic cardiomyopathy (HCM), Ellims *et al.* investigated the correlations of macroscopic myocardial fibrosis (assessed with LGE CMR) and diffuse myocardial fibrosis (assessed with post-contrast T1 mapping) with LV function and genotype.[24] The presence of LGE was associated with LVEF and presence of LV outflow tract obstruction whereas shorter post-contrast T1-mapping values (more diffuse fibrosis) were significantly associated with LV diastolic dysfunction and dyspnoea symptoms. Interestingly, patients with identifiable HCM genetic mutations showed larger extent of LGE (7.9 ± 8.6 vs. 3.1 ± 4.3%, P = 0.03) but longer post-contrast T1-mapping values (498 ± 81 vs. 451 ± 70 ms, P = 0.03) compared with patients without mutations. Using LGE CMR, Nadel *et al.* investigated in 106 patients with biopsy-proven extracardiac or cardiac sarcoidosis the association between the presence of

(više difuzne fibroze) povezane s dijastoličkom funkcijom LK i simptomima zaduhe. Zanimljivo je da su pacijenti s prepoznatljivim genskim mutacijama HCM imali širi opseg LGE (7,9 ± 8,6 prema 3,1 ± 4,3%; *P* = 0,03), ali duže vrijednosti mapiranja T1 nakon kontrasta (498 ± 81 prema 451 ± 70 msec; *P* = 0,03) u usporedbi s pacijentima bez mutacija. Nadel *i sur.* su uporabom LGE MRI-ja srca u 106 pacijenata s biopsijom dokazanom ekstrakardijalnom ili kardijalnom sarkoidozom istražili povezanost prisutnosti fokalne makroskopske fibroze i pojave zajedničkoga ciljnog ishoda (ukupna smrtnost, iznenadna srčana smrt, ventrikulska tahikardija ili fibrilacija).[25] U 32 pacijenta (30 %) LGE MRI srca pokazao je fokalnu fibrozu miokarda, koja je bila nejednako rasprostranjena u većine pacijenata (72 %), za razliku od subepikardijalne (59 %) i distribucije u srednjem segmentu (25 %). Tijekom prosječnog razdoblja praćenja od 37 mjeseci 16 je pacijenata dostiglo taj zajednički ciljni ishod. Prisutnost fokalne fibroze miokarda na LGE MRI-ju srca bila je neovisno povezana sa zajedničkim ciljnim ishodom (HR 12,52, 95% CI 1,35 – 116,18; *P* = 0,03). Banypersad *i sur.* u 100 pacijenata sa sistemskom amiloidozom lakih lanaca procijenili su prognostičku vrijednosti ECV-a, nativne vrijednosti T1 prije kontrastnoga sredstva te vrijednosti nakon kontrastnoga sredstva.[26] Tijekom prosječnog razdoblja praćenja od 23 mjeseca 25 % bolesnika je preminulo. Prag ECV-a ≥ 0,45 (HR 3,84, 95 % CI 1,53 – 9,61; *P* = 0,004) i prag vrijednosti nativnog vremena T1 ≥1044 msek. (HR 5,39, 95 % CI 1,24–23,4; *P* = 0,02) neovisno su povezani s ukupnom smrtnosti, dok vrijednosti T1 nakon kontrastnoga sredstva nisu poslužile za predviđanje smrti.

Metode oslikavanja uz primjenu radioizotopa

Nekoliko je istraživanja proučavalo obilježja upale i nakupljanja lipida u stijenci arterije s pomoću nuklearnomedicinskih postupaka oslikavanja u pacijenata s čimbenicima kardiovaskularnog rizika.[27,28] Van der Falk *i sur.* nastojali su procijeniti ulogu leukocita u aterogenezi izvođenjem jednofotonske emisijske računalne tomografije (SPECT)-CT s mononuklearima periferne krvi označenima s 99m tehnecijem (PBMC).[27] U skupini od 10 pacijenata s poznatim kardiovaskularnim bolestima i pet zdravih pacijenata uočeno je značajno nakupljanje PBMC-a kod pacijenata s uznapredovalim aterosklerotskim lezijama. Ovo je nov pristup oslikavanju sa svrhom vizualiziranja migracije leukocita i nakupljanja PBMC-a pri aterosklerozi u ljudi, što će možda poslužiti i kao potpora strategijama za regrutiranje leukocita kao terapijskog cilja u pacijenata s kardiovaskularnim bolestima. Van Wik *i sur.* Pokazali su da afereza lipoproteina dovodi do znatnog smanjenja upale arterijske stijenke u pacijenata s obiteljskom hiperkolesterolemijom (FH) karakteriziranom jako povišenim razinama LDL kolesterola.[28] Pozitronska emisijska tomografija (PET) s 18-F-fluorodeoksiglukozom (FDG) primijenjena je kako bi se procijenio *target-to-background ratio* (TBR) pohrane FDG-a u arterijskoj stijenci u 24 pacijenta s FH te u 14 normolipemičnih pacijenata. Drugo PET oslikavanje provedeno je tri dana poslije u 12 pacijenata u kojih je obavljena afereza lipoproteina te je uočen značajan pad u TBR u usporedbi s prvim oslikavanjem (2,05 ± 0,31 prema 1,91 ± 0,33; *P* < 0,02). Dobiveni rezultati daju naslutiti kako lipoproteini s apoproteinom B imaju ulogu

focal macroscopic fibrosis and occurrence of the composite endpoint all-cause mortality, sudden cardiac death, ventricular tachycarrhyhtmia or ventricular fibrillation.[25] Thirty-two (30%) patients showed focal myocardial fibrosis on LGE CMR which was of patchy distribution in the majority of patients (72%) followed by subepicardial (59%) and midwall (25%) distribution. During a mean follow-up of 37 months, 16 patients reached this composite endpoint. The presence of focal myocardial fibrosis on LGE CMR was independently associated with the composite endpoint (HR 12.52, 95% CI 1.35–116.18, *P* = 0.03). In 100 patients with systemic light-chain amyloidosis, Banypersad and coworkers evaluated the prognostic value of ECV, pre-contrast (native), and post-contrast T1 values.[26] During a median follow-up of 23 months, 25% of patients died. A cut-off value of ECV ≥0.45 (HR 3.84, 95% CI 1.53–9.61, *P* = 0.004) and a cut-off value of native T1 time ≥1044 ms (HR 5.39, 95% CI 1.24–23.4, *P* = 0.02) were independently associated with all-cause mortality, whereas post-contrast T1 mapping values were not predictive of mortality.

Nuclear imaging

In patients with cardiovascular risk factors, characterization of inflammation and lipid accumulation in the arterial wall using nuclear imaging has been the target of several studies.[27,28] Van der Falk *et al.* aimed at assessing the role of leukocytes in atherogenesis by performing single photon emission computed tomography (SPECT)-CT with ^{99m}Technetium-labeled peripheral blood mononuclear cells (PBMC).[27] In 10 patients with known cardiovascular disease and 5 healthy controls, a markedly enhanced accumulation of PBMC was found in patients with advanced atherosclerotic lesions. This represents a novel-imaging approach to visualize leukocyte migration and PBMC accumulation to atherosclerosis in humans, potentially lending support to strategies aimed at attenuating leukocyte recruitment as a therapeutic target in patients with cardiovascular disease. Van Wik *et al.* demonstrated that lipoprotein apheresis leads to a marked reduction of arterial wall inflammation in patients with familial hypercholesterolaemia (FH) characterized by severely elevated plasma low-density lipoprotein cholesterol levels.[28] 18-F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) was used to assess the target-to-background ratio (TBR) of FDG uptake within the arterial wall in 24 patients with known FH and in 14 normolipidemic controls. A second PET scan was acquired after 3 days in 12 patients in whom lipoprotein apheresis was performed and demonstrated a significant reduction of TBR compared with the baseline scan (2.05 ± 0.31 vs. 1.91 ± 0.33; *P* < 0.02). These suggest that apoprotein B-containing lipoproteins play a role in arterial wall inflammation and support the concept of a beneficial effect of lipoprotein apheresis.

In addition, Moon *et al.* sought to investigate the added prognostic value of FDG-PET over the FRS and carotid intima-media thickness (CIMT) for the prediction of future cardio-cerebrovascular events.[29] Carotid FDG uptake and CIMT were measured in 1089 asymptomatic adults who underwent PET imaging. Cardio-cerebrovascular events occurred in 19 participants (1.74%) during an average follow-up of 4.2 years. Multivariate Cox regression analysis revealed that high ca-

u upali arterijske stijenke te govore u prilog ideji o povoljnom učinku afereze lipoproteina.

Moon *i sur.* pokušali su istražiti dodatnu prognostičku vrijednost FDG-PET-a u odnosu prema FRS-u te debljinu intime-medije karotida (CIMT) za predviđanje budućih kardiocerebrovaskularnih događaja.[29] Pohrana FDG-a u karotidnoj arteriji i CIMT izmjereni su u 1089 asimptomatskih odraslih pacijenata u kojih je obavljeno oslikavanje PET-om. U 19 ispitanika (1,74 %) nastupili su kardiocerebrovaskularni događaji u prosječnom razdoblju praćenja od 4,2 godine. Coxovom multivarijatnom analizom otkrivena je visoka pohrana FDG-a u karotidnoj arteriji (HR 2,98; 95 % CI 1,17 – 7,62; *P* = 0,022) i visoka vrijednost CIMT-a (HR 2,82; 95 % CI 1,13 – 7,03; *P* = 0,026) kao neovisni prediktor tih događaja. Pohrana FDG-a u karotidnoj arteriji također je unaprijedila razlikovanje prediktora rizika kada se doda procjena FRS-om, neovisno o CIMT-u.

U bolesnika sa sumnjom na akutni koronarni sindrom i negativnim biomarkerima postojeće smjernice preporučuju rutinsku primjenu testiranja opterećenjem.[30] Malo je poznato o potencijalnoj ulozi perfuzijske scintigrafije miokarda (MPI) u takvom okruženju. Cremer *i sur.* istražili su uporabu SPECT-MPI-ja za otkrivanje ishemije, njegovu prognostičku vrijednost za kratkoročne događaje te utjecaj na posljedični postupak.[31] Od 5354 pacijenta koji su upućeni s odjela hitne pomoći nakon što su pretrage dokazale negativnu vrijednost troponina T i nedijagnostički EKG, samo 6,1 % pacijenata s vrijednostima TIMI bodovne ljestvice ≤ 2 imalo je > 5 % ishemijskog miokarda, dok je 19,6 % pacijenata s vrijednostima prema TIMI ≥ 3 imalo > 5 %. Kratkoročni neželjeni događaji bili su rijetki unutar razdoblja od 30 dana, sa samo 0,1 % smrtnosti i 0,1 % pacijenata u kojih je provedena revaskularizacija zbog akutnog infarkta miokarda. Takvi rezultati daju naslutiti kako bi SPECT-MPI prije otpusta, a nakon dvaju negativnih nalaza troponina trebao biti od koristi u pacijenata s iznosom TIMI ≥ 3.

Kada je riječ o akutnom infarktu miokarda, pokazalo se kako FDG-PET može detektirati upalu u akutnom infarktu miokarda ako su integrirane informacije o kasnom pojačanju kontrasta (tkivo ožiljka) dobivene popratnim MRI-jem ili CT-om srca. Wollenweber *i sur.* proveli su ovaj koncept u 15 pacijenata rano nakon infarkta miokarda obavljanjem PET-a i MRI-ja srca unutar 7 dana od prvog infarkta miokarda.[32] Svi su pacijenti liječeni heparinom kako bi se spriječila pohrana FDG-a u dislociranom dijelu miokarda. Metabolička stopa glukoze znatno je povećana kod miokarda zahvaćena infarktom u odnosu prema distalnom dijelu miokarda (2,0 prema 0,4 mg/min na 100 mL; *P* = 0,0001). Iznos FDG-a bio je najveći u segmentima s LGE u usporedbi s onima samo s edemom te s udaljenim miokardom (2,0 prema 1,8 naspram 0,4; *P* < 0,0001). Stoga se čini kako povećana pohrana FDG-a nakon supresije miocita potaknute heparinom, odražava upalnu aktivnost u tkivu miokarda zahvaćena akutnim infarktom.

Teret zračenja povezan s nuklearnim oslikavanjem i dalje je razlog za zabrinutost te je bio predmet istraživačke skupine INCAPS, koja je provela presječno istraživanje radionuklidnih protokola MPI-ja u 308 nuklearnih kardioloških laboratorija u 65 zemalja diljem svijeta te je pritom karakterizirala razine zračenja u pacijenata te 'najbolju praksu' pri njezinoj optimizaciji.[33] Učinkovita doza zračenja u pacijenata kretala se izrotid FDG uptake (HR 2.98; 95% CI 1.17–7.62; *P* = 0.022) and high CIMT (HR 2.82; 95% CI 1.13–7.03; *P* = 0.026) were independent predictors of these events. Furthermore, carotid FDG uptake improved discrimination of risk prediction when added to the FRS independently CIMT.

In patients with suspected acute coronary syndrome and negative cardiac biomarkers routine exercise testing is recommended by current guidelines.[30] Little is known on the potential role of nuclear myocardial perfusion imaging (MPI) in this context. Cremer *et al.* reported on the yield of SPECT-MPI for detecting ischaemia, its prognostic value for short-term events, and its impact on downstream resource utilization.[31] Among 5354 patients referred from the emergency department after negative troponin T tests and non-diagnostic ECGs, only 6.1% of patients with a thrombolysis in myocardial infarction (TIMI) score ≤2 presented with >5% ischaemic myocardium, while 19.6% of patients with TIMI scores ≥3 had >5%. Furthermore, short-term adverse events were rare at 30 days with only 0.1% mortality and 0.1% of patients undergoing revascularization for acute MI. These findings suggest that SPECT-MPI before discharge after two negative troponins should be helpful in patients with TIMI scores ≥3.

In the field of acute MI, it has been shown that FDG-PET may be able to detect inflammation in the acutely infarcted myocardium, if information on late contrast enhancement (scar tissue) from concomitant CMR or CT is integrated. Wollenweber *et al.* have translated these concepts into 15 patients early after MI by performing PET and CMR within 7 days of first MI.[32] All patients underwent heparin pre-treatment to suppress FDG uptake in remote myocardium. The metabolic rate of glucose was significantly increased in infarcted vs. remote myocardium (2.0 vs. 0.4 mg/min per 100 mL; *P* = 0.0001). Regionally, FDG score was highest in segments with LGE vs. oedema only and to remote myocardium (2.0 vs. 1.8 vs. 0.4; *P* < 0.0001). Thus, increased FDG uptake after heparin-induced suppression of myocyte uptake appears to reflect inflammatory activity in acutely infarcted myocardial tissue.

Finally, the radiation burden associated with nuclear imaging remains of concern and was the objective of the INCAPS Investigators Group which conducted an observational cross-sectional study of nuclear MPI protocols in 308 nuclear cardiology laboratories in 65 countries around the world, characterizing patient radiation doses and the use of radiation optimizing 'best practices'.[33] Patient effective radiation dose ranged between 0.8 and 35.6 mSv (median 10.0 mSv). Average laboratory effective dose ranged from 2.2 to 24.4 mSv (median 10.4 mSv) and only 30% of all laboratories achieved a median effective dose of ≤9 mSv as recommended by guidelines. The lowest effective dose (median 8.0 mSv) was administered in Europe, coinciding with the highest best-practice adherence rate.

Integration or fusion of different imaging modalities

The number of studies published on the use of integrated or fusion imaging is increasing, indicating increasing use of integrated PET-CT and PET-MRI equipment, but also the fusion

među 0,8 i 35,6 mSv (medijan 10,0 mSv). Prosječna učinkovita doza u laboratoriju kretala se između 2,2 i 24,4 mSv (medijan 10,4 mSv), a samo je 30 % laboratorija imalo učinkovitu dozu ≤ 9 mSv, koju preporučuju smjernice. Najniža učinkovita doza (medijan 8,0 mSv) zabilježena je u Europi, gdje je zabilježena i najviša stopa pridržavanja najbolje prakse.

Integracija ili spajanje različitih vrsta oslikavanja

Broj se objavljenih istraživanja o integriranom ili fuzijskom oslikavanju povećava, što potvrđuje porast primjene integrirane PET-CT i PET-MRI opreme, ali i spajanje neovisno prikupljenih podataka, primjerice, iz SPECT-a i fluoroskopije. Zhou *i sur.* razvili su trodimenzionalnu fuzijsku opremu s namjerom spajanja anatomije venskog sustava lijeve klijetke (dobivene fluoroskopijom) sa SPECT-MPI (kako bi procijenili ožiljak miokarda), što bi poslužilo kao vodič za postavljanje elektroda prilikom CRT-a.[34]

Fuzijsko oslikavanje PET-CT-om primijenjeno je u pacijenata sa sumnjom na KBS.[35,36] Valenta *i sur.* pregledali su 24 pacijenta koristeći se PET-CT-om i amonijakom N13 kako bi procijenili različite varijable tijeka krvi u miokardu (rezerva protoka i gradijenti protoka) povezanih s CTCA-om, što je dovelo do boljeg razumijevanja hemodinamskoga značenja koronarnih stenoza.[35] Dey *i sur.* predočili su rezultate o PET-CT-u u 51 pacijenta: CTCA (analiziran kvantitativno) spojen je s rezervom protoka miokarda (dobivenog opterećenjem u mirovanju PET-om s amonijakom N13).[36] Predviđanja o smanjenju rezerve protoka

of independently obtained data from (for example) SPECT and fluoroscopy. Zhou and colleagues developed a 3D fusion tool kit to fuse LV venous anatomy (derived from fluoroscopy) with SPECT-MPI (to assess myocardial scar) to guide LV lead placement in CRT.[34]

Fusion imaging with PET-CT has been applied in patients with suspected CAD.[35,36] Valenta and colleagues evaluated 24 patients with PET-CT using N13-ammonia to assess different myocardial blood flow variables (flow reserve and flow gradients), which were related with CTCA, resulting in better understanding of the haemodynamic significance of coronary stenoses.[35] Dey *et al.* reported on PET-CT data from 51 patients: CTCA (quantitatively analysed) was fused with myocardial flow reserve (derived from rest-stress N13-ammonia PET).[36] Prediction of reduced myocardial flow reserve (indicating ischaemia) was optimal when CTCA stenosis severity was integrated with various other CTCA variables, including total (non-calcified) plaque burden. These findings indicate that an integrated CTCA score (including stenosis severity, total plaque burden, and plaque constitution) may better predict reduced myocardial flow reserve.

Ahmed *et al.* explored the utility of ^{18}F-FDG-PET-CT in the diagnosis of cardiac implantable electronic device generator pocket infection.[37] To this end, 46 patients with suspected generator pocket infection and 40 without any infection underwent PET imaging, and FDG activity in the region of the generator pocket (**Figure 4**) was expressed as a semi-quantitative ratio (SQR) defined as the maximum count rate around the generator divided by the count rate between normal right

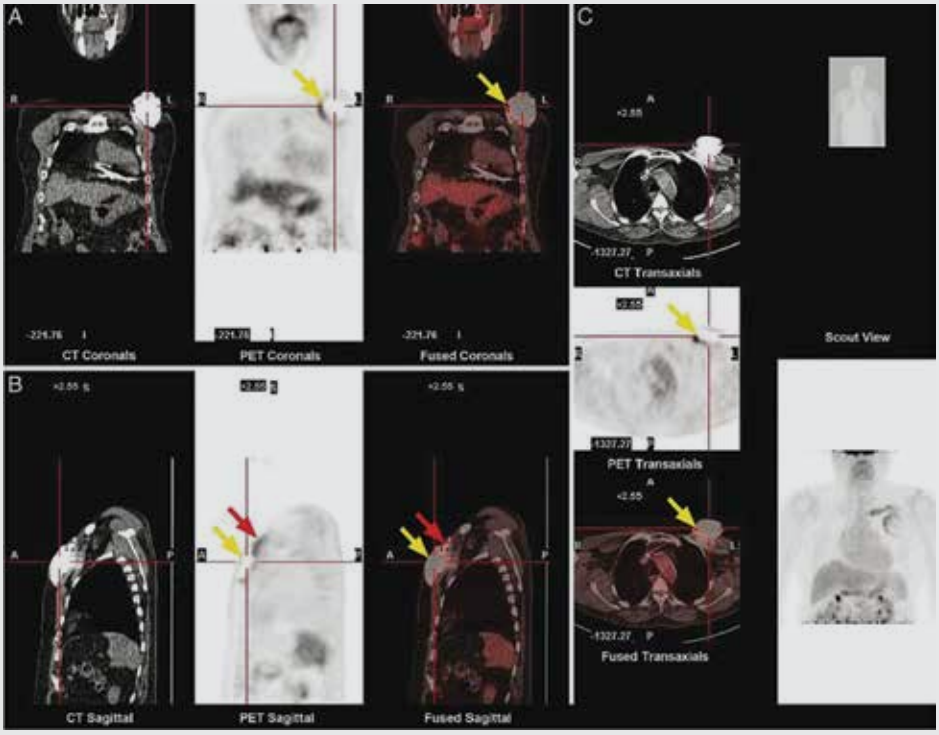

FIGURE 4. PET-CT in suspected device pocket infection. Example of a positive ^{18}F-FDG PET/CT scan in a patient with pain at the generator pocket site. (A) Increased FDG uptake is seen in the region of the left pre-pectoral pocket on the coronal views (yellow arrows). (B) In the sagittal plane, increased FDG uptake can be seen on the muscular aspect of the pre-pectoral generator (yellow arrows) and along the proximal portion of the leads (red arrows). (C) Increased FDG uptake visualized on the muscular aspect of the generator pocket (yellow arrows). Reproduced with permission from Ahmed *et al.*[37]

toka miokarda (što znači ishemiju) bila su optimalna kada je težina stenoze dobivena s pomoću CTCA integrirana s drugim varijablama dobivenim primjenom CTCA, uključujući potpuno (nekalcificirajuće) opterećenje plaka. Ta otkrića pokazuju da integrirani iznos CTCA (uključujući i težinu stenoze, ukupno opterećenje i konstituciju plaka) možda može poslužiti kao bolji prediktor redukcije u rezervi protoka miokarda.

Ahmed *i sur.* istražili su primjenjivost[18] F-FDG-PET-CT-a u dijagnozi infekcije lože generatora ugradbenoga elektroničkog srčanog uređaja.[37] S tom je svrhom provedeno oslikavanje primjenom PET-a u 46 pacijenata u kojih se sumnjalo na infekciju lože generatora i u 40 pacijenata bez infekcije, pri čemu je aktivnost FDG-a u području lože generatora (**slika 4**) izražena kao polukvantitativni omjer (SQR) određen kao maksimalna stopa mjerenja oko generatora podijeljena sa stopom mjerenja između normalnoga desnog i lijevog plućnog parenhima. Pacijenti u kojih se sumnjalo na infekciju lože generatora i koji su trebali vađenje generatora imali su mnogo veću FDG aktivnost negoli kontrolna skupina (SQR 4,80 prema 1,40 prema 1,10; $P < 0,001$). Analizom ROC-krivulje autori su izračunali optimalni prag SQR u iznosu od > 2,0 kojim se dobiva vrlo visoka osjetljivost i specifičnost od 97 i 98 %. Ti rezultati pokazuju visoke dijagnostičke performanse i ističu potencijalnu primjenjivost FDG-PET-a za otkrivanje rane infekcije lože generatora ugradbenoga elektroničkoga srčanog uređaja.

and left lung parenchyma. Patients with suspected generator pocket infection that required generator extraction had significantly higher FDG activity compared with those that did not, and with controls (SQR 4.80 vs. 1.40 vs. 1.10, $P < 0.001$). From receiver operator characteristic curve analysis, the authors calculated an optimal SQR cut-off value of >2.0, yielding a very high sensitivity and specificity of 97 and 98%, respectively. These results demonstrate a high diagnostic performance and highlight the potential utility of FDG-PET for the detection of early cardiac implantable electronic device generator pocket infection.

Fusion imaging of CT and echocardiography in heart valve disease was reported by Kamperidis *et al.*[38] The authors addressed the topic of low gradient, but severe aortic stenosis in patients with preserved LVEF; this 'mismatch' between the low gradient over the valve (indicating no stenosis) but the small valve area (indicating severe stenosis) may be related to the assumption of a circular shape of the LV outflow tract with 2D echocardiography (which in fact often may have an elliptical shape). Since this parameter contributes significantly to the calculation of the aortic valve area (**Figure 5**), this may contribute to errors in classification of severity of aortic stenosis. The LV outflow tract may be more accurately detected from CT (anatomical) imaging by direct planimetry, and fusion of the CT-derived LV outflow tract area with the echo Doppler data may result in significant reclassification of

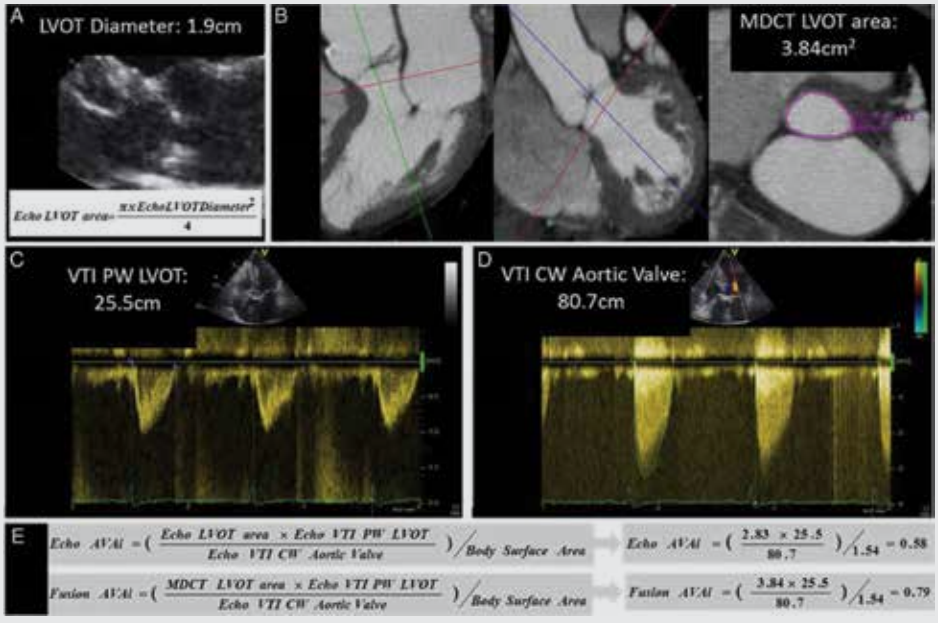

FIGURE 5. Quantification of aortic valve area using fusion imaging in aortic stenosis. Current clinical practice, 2-dimensional and Doppler echocardiography are used to calculate the aortic valve area (**panels A, C, D and E**): the LV outflow tract (LVOT) diameter is measured from the parasternal long-axis view and the flow of the LVOT and gradient of aortic valve are measured with pulsed and continuous wave Doppler. By introducing the true cross-sectional area of the LVOT measured with MDCT (**panel B**) into the Bernoulli equation (**panel E**), the aortic valve area fusion is calculated. In this particular example, an aortic valve area index of 0.58 cm^2/m^2 calculated with echocardiography (Echo AVAi) indicates severe aortic stenosis whereas by using the MDCT cross-sectional area of the LVOT, the aortic valve area index (Fusion AVAi) increases to 0.79 cm^2/m^2 indicating moderate aortic stenosis. Reproduced with permission from Kamperidis *et al.*[38]

O fuzijskom oslikavanju primjenom CT-a i ehokardiografije u valvulnim bolestima izvijestili su Kamperidis *i sur.*[38] Autori su istraživali temu niskog gradijenta kod teške aortne stenoze u pacijenata s očuvanom LVEF. Ovaj nerazmjer između niskog gradijenta nad zalistkom (upućuje da nema stenoze), ali malom valvulnom površinom (upućuje na tešku stenozu) može biti povezan s procjenom cirkularnog oblika izlaznog dijela LK kod 2D ehokardiografije (koji zapravo često može imati eliptični oblik). Kako ova varijabla znatno pridonosi izračunu površine aortne valvule (**slika 5**), ovo može pridonijeti pogreški u klasifikaciji težine aortne stenoze. Izlazni dio LK može se preciznije anatomski oslikati direktnom planimetrijskom metodom s pomoću CT-a te fuzija tako dobivene površine s doplerskim podatcima dobivenima ehokardiografijom može značajno reklasificirati slučajeve nepravilno klasificirane teške aortne stenoze. U 191 pacijenta s teškom aortnom stenozom (površina aortne valvule indeksirana sukladno površini tijela < 0,6 cm^2/m^2) i očuvanom LVEF (≥ 50 %) primijenjen je fuzijski pristup kojim je reklasificirano 52 % pacijenata s niskim gradijentom, ali teškom aortnom stenozom i očuvanom LVEF u srednje težak stupanj aortne stenoze (**slika 5**).

inconsistently graded severe aortic stenosis. In 191 patients with severe aortic valve stenosis (according to the aortic valve area indexed for body surface area being <0.6 cm^2/m^2) and preserved LVEF (≥50%), this fusion approach was applied and reclassified 52% of patients with low gradient but severe aortic stenosis and preserved LVEF into moderate aortic stenosis (**Figure 5**).

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